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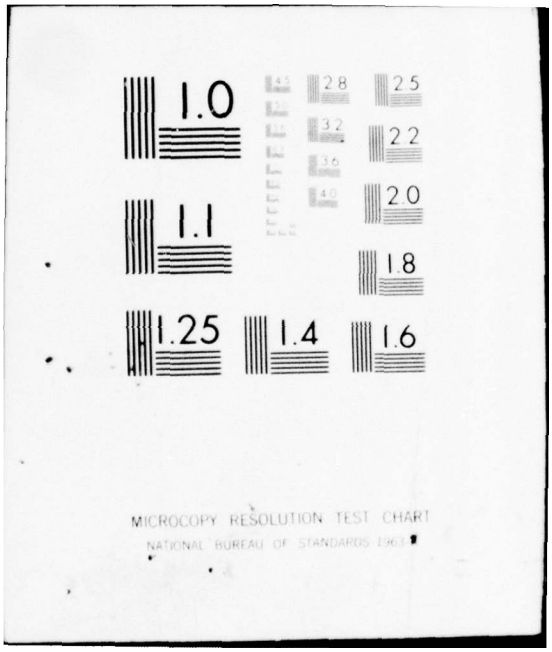
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TECHNICAL REPORT NO. 102

Abstract Reference List
Reviews of Pertinent Literature
in Shock

L. B. Hinshaw

University of Oklahoma Health Sciences Center
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Oklahoma City, Oklahoma

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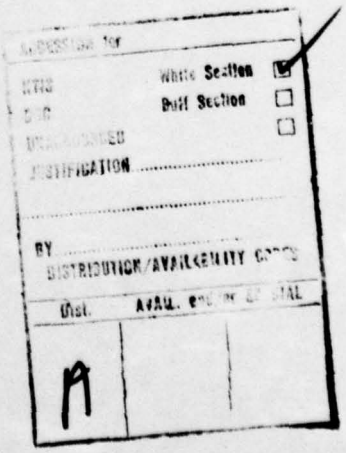

INDEX

1. Use of Vasoactive Drugs in the Treatment of Shock. James L. Berk, M.D. Surg. Clin. N. Amer. 55: 721-728, 1975.

   The effective use of vasoactive drugs in shock requires an understanding of the pathophysiologic mechanisms involved in the various types and stages of shock and knowledge of the specific pharmacologic effects of each drug in the abnormal state. Vasoactive drugs should be used after the primary and secondary causes of shock have been corrected. Specific vasoactive drugs should be selected on the basis of measured hemodynamic abnormalities. A combination of vasoactive drugs to achieve a balance between the cardiac and microcirculatory effects has been suggested. In addition to those discussed, examples are norepinephrine and isoproterenol, dopamine and isoproterenol, and phenoxybenzamine or phentolamine and dopamine or norepinephrine. Dopamine in conjunction with intra-aortic balloon counterpulsation has also been used. As yet, there is insufficient evidence to suggest which of these combinations is the most effective but selective organ system control is possible and in the future this type of therapy should be rewarding.

2. Monitoring the Patient in Shock. James L. Berk, M.D. Surg. Clin. N. Amer. 55: 713-720, 1975.

   In critically ill patients there is frequently more than one problem, which may not be obvious, contributing to the shock state. The history, physical exam, and monitoring devices may not be reliable individually, but must be considered together and interpreted in the light of the pathophysiologic mechanisms involved.

   A plan for monitoring and treating critically ill patients is outlined. The advantages and limitations of various monitoring techniques are discussed.

3. Use of Balloon Flotation Catheters in Critically Ill Patients. H. J. C. Swan, M.D., Ph.D., and William Ganz, M.D., C.Sc. Surg. Clin. N. Amer. 55: 501-520, 1975.

   In summary, balloon flotation catheterization of the central circulation provides data in patient management which are meaningful and important. It has allowed the application of sound physiologic principles to the understanding of the circulatory abnormalities characterizing an illness in an individual patient, and provides a rational basis for selection of therapy with objective, quantiative assessment of patient response. The procedures are simple, the complication rate is low, and the information highly relevant to clinical care.

4. Cardiac Output Determinations in Surgical Patients. George W. Tietjen, M.D., Frank E. Gump, M.D., and John M. Kinney, M.D. Surg. Clin. N. Amer. 55: 521-529, 1975.

   The value of cardiac output determinations in evaluating patients for cardiac surgery has been long recognized. Recently, however, cardiac surgeons have begun to monitor cardiac output during and after cardiac surgery both as a guide to postoperative management and as an index of the efficacy of the surgical procedure.

   Serial cardiac output determinations would be of value to guide the clinician in fluid administration and the use of cardiotonic drugs in the critically ill patient.

Finally, cardiac output measurements are seeing application in the preoperative evaluation of the high risk elderly patient. Noting that cardiac reserve is a major factor in survival of patients over 65 years of age, Del Guercio and colleagues performed intensive hemodynamic studies in elderly preoperative patients. They devised a new physiologic variable (ventricular mixing volume), which is an expression of the shape, splay, and area under the dye-dilution curve. When ventricular mixing volume is plotted against stroke work, a zone of abnormal ventricular function was evident. None of eight patients who preoperatively fell into this zone survived the surgical procedure.

In conclusion, then, it becomes apparent that the routine clinical assessment of the critically ill patient is no longer adequate, and it is hoped that through a more complete physiologic evaluation, patient survival will improve.

5. Peripheral Vasodilators in Low Cardiac Output States. James S. Forrester, M.D., Protasio L. da Luz, M.D., and Danu Chatterjee, M.B., M.R.C.P. Surg. Clin. N. Amer. 55: 531-544, 1975.

   In summary, the use of peripheral vasodilators represents a major advance in the therapy of heart failure of all causes and is of particular value in treatment of the critically ill patient. Depressed cardiac output, the hemodynamic cause of forward failure, is increased by 25 per cent; and elevated pulmonary capillary pressure, the hemodynamic cause of backward failure, can frequently be reduced to within the normal range following vasodilator administration. When properly administered, vasodilators reduce coronary blood flow and myocardial oxygen demand by approximately equal magnitude, and for this reason the balance between myocardial oxygen supply and demand is not adversely affected, although blood pressure may be reduced. The significant side effect of vasodilator administration, induction of hypotension, can be controlled by careful drug administration, and substantial hemodynamic improvement frequently occurs without any alteration in systemic arterial pressure. The mode of vasodilator administration may be intravenous, sublingual, or topical. Intravenous therapy is to be preferred in the critically ill patient in whom hemodynamic measurements are available, since the drug dosage can be effectively altered in relationship to observed hemodynamics. In the less critically ill patient, and in those institutions in which hemodynamic monitoring is not available, the use of isosorbide dinitrate or possibly nitroglycerin ointment may allow the physician to administer this particularly potent therapy to patients with heart failure with little risk of serious complications.

6. The Effect of Estrogen on the Vascular Endothelium and Its Possible Relation to Thrombosis. Torsten Almén, M.D., Michael Härtel, M.D., Göran Nylander, M.D., and Hans Olivercrona, M.D., Malmö, Sweden. Surg. Gynec. Obstet. Surg. Gynec. Obstet. 140:938-940, 1975.

   The cause of venous thrombosis is far from clear. The three etiologic factors laid down by Virchow in his well known triad--stasis, alterations in the coagulability of the blood and injury to the vascular wall--are still valid. Any of these three factors may be involved in the thrombogenesis of the patient.

The effect of estrogen on the permeability of the endothelium of aorta has been studied in the rat. The endothelium was subjected to different forms of chemical injury, and its permeability to silver ions was estimated in rats in a control group and in rats after estrogen treatment. In rats subjected to estrogen treatment, the degree of silver penetration through the endothelium was significantly higher than in untreated rats. This was interpreted as an increased vulnerability of the endothelium after estrogen treatment. Thrombosis in females using oral contraceptives often has an aberrant localization. These findings lead to a theory that an endothelial factor may be involved in the pathogenesis of this form of thrombosis.

7. Peripheral Vascular Actions of Glucocorticoids and Their Relationship to Protection in Circulatory Shock. Burton M. Altura and Bella T. Altura. J. Pharm. Exptl. Therap. 190: 300-315, 1974.

The present study was undertaken to determine whether massive doses of hydrocortisone sodium succinate (HC) and methylprednisolone sodium succinate (MP): 1) alter microvascular lumen diameters in the splanchnic microcirculation and/or arteriolar reactivity to constrictor catecholamines and vasopressin in the microcirculation; 2) are effective as therapeutic regimens after circulatory shock is induced by different means (e.g., hemorrhage, bowel ischemia); 3) alter reactivity of isolated arteries to various contractile agents; and 4) alter the early reticulendothelial system (RES) phagocytic depression characteristic of circulatory shock syndromes. Locally administered as well as systemically administered pharmacologic doses of both HC and MP failed to alter microvascular lumen diameters of normal rat arterioles. However, both HC and MP effectively restored the severely constricted arterioles of shocked rats to near normal during as well as after i.v. infusion. Both steroids (in pharmacologic doses) dose dependently inhibit epinephrine-, norepinephrine- and vasopressin-induced contractions as well as displace the log dose-response curves of these vasoactive agents, nonspecifically, to the right on in vivo arterioles as well as in vitro on the arteries. HC and MP, in pharmacologic concentrations, attempted contractile responses of aortic strips induced by angiotension, serotonin, potassium and calcium. HC (300 mg/kg) and MP (30 mg/kg) not only significantly improved survival rates of rats subjected to two different types of circulatory shock, when administered after the shock was induced, but effectively restored RES function to normal. These data suggest that pharmacologic doses of glucocorticoids may confer protection in shock by: 1) preventing the intense peripheral vasoconstrictor action of the many vasoactive constrictor substances released in shock and 2) aiding in the restoration of normal RES phagocytic function.

8. Pulmonary and Hematologic Disturbances During Septic Shock. G. F. Milligan, F.R.C.S., J. A. E. MacDonald, F.R.C.S., Anne Mellon, F.F.A.R.C.S., and I. McA. Ledingham, M.D., Glasgow, Scotland. Surg. Gynec. Obstet. 138: 43-49, 1974.

Twenty-one patients in a state of septic shock have been studies. Nineteen patients had a marked reduction in platelet count with associated coagulation deficiencies and evidence of intravascular coagulation. Evidence of pulmonary gas exchange defect was present in all but one of the patients, and moderate moderate to severe radiologic changes were observed in all but four patients.

An association between the hematologic and pulmonary disturbances is suggested. The judicious use of positive pressure ventilation appears to halt the progressive nature of the pulmonary gas exchange defect until the underlying process resolves spontaneously.

9. Direct Influence of Endotoxin on Cellular Respiration. Alden H. Harken, M.D., Richard S. Lillo, B.S., and Howard V. Hufnagel, B.S. Surg. Gynec. Obstet. 140:858-860, 1975.

   Hepatocyte oxygen consumption was evaluated in vitro in 70 rabbits. In selected instances, Escherichia coli endotoxin was added to a chamber containing either rabbit hepatocytes or hepatocyte homogenates. Endotoxin directly depressed the respiration of intact rabbit hepatocytes. Endotoxin also decreased the oxygen consumption of hepatocyte homogenates. The intact cell membrane is not an effective barrier to the deleterious effect of endotoxin. A patient in a state of endotoxic shock, in addition to having a hemodynamic derangement, probably has circulating toxins that directly render cellular oxidative phosphorylatin less efficient.

10. Antiendotoxic Effect of Water-Soluble Analogs of Glucocorticoids. Peter R. Erve, Ph.D., Wayne Earnest, M.S., and William Schumer, M.D. J. Surg. Res. 18: 567-569, 1975.

    The results of this study indicate that in the rat the antiendotoxic action of hydrocortisone, methylprednisolone, or dexamethasone is not affected by the nature of the salt radical employed to render these steroids water soluble. Also, the administration of methylprednisolone succinate and dexamethasone phosphate in concert protects in a simple additive manner.

11. Prevention by glucocorticoids of disseminated intravascular coagulation induced by endotoxin: mechanisms. Jean-Gilles Latour and Claudette Leger. J. Lab. Clin. Med. 85: 934-949, 1975.

    The therapeutic efficiency of two glucocorticoids (hydrocortisone and dexamethasone) on endotoxin-induced intravascular coagulation was investigated in the rat. Coagulation and platelet aggregation studies were performed and plasminogen was assayed. Our results indicate that pretreatment of the animals with large doses of these steroids within a few hours prior to endotoxin totally prevents the consumption in Hageman factor, measurable contact product activity, platelets, fibrinogen, plasminogen, and the loss in platelet aggregability and serotonin. In addition to this, the hypercoagulable state consecutive to endotoxin, characterized here by shortenings in the partial thromboplastin and recalcification times and by an increase in the availability of platelet procoagulant activity, was also totally prevented by the steroid pretreatment. On the other hand, it is shown that these glucocorticoids do not interfere in the normal rat with platelet aggregation (tested with thrombin, adenosine diphosphate, and collagen), but with the availability of platelet procoagulant activity. This last phenomenon, in addition to that of an interference in vivo with the mechanisms of activation of Hageman factor, are believed to be responsible for prevention by glucocorticoids of endotoxin-induced disseminated intravascular coagulation.

12. Septic Lung and Shock Lung in Man. George H. A. Clowes, Jr., M.F., Erwin Hirsch, M.D., Lester Williams, M.D., Edward Kwasnik, B.S., Thomas F. O'Donnel, M.D., Peter Cuevas, M.D.V.K. Saini, M.D., Iradj Moradi, M.D., Moreza Farizan, M.D., Calvin Saravis, Ph.D., Michael Stone, B.S., Julian Kuffler, B.S. Anns. Surg. 181: 681-692, 1975.

Two series of patients were studied by serial measurements of blood gas exchange and pulmonary hemodynamics to compare the relative importance of hemorrhagic shock and sepsis as causes of pulmonary dysfunction and to evaluate the dangers of respiratory failure in post traumatic patients. There were 27 patients who had sustained profound hemorrhagic shock and massive blood replacement averaging 9.7 liters and 38 patients who suffered general peritonitis or other forms of fulminating nonthoracic sepsis. All were supported by endotrachael intubation and volume controlled ventilators. The overall mortality for the post shock patients without sepsis was 12% while in the septic patients it was 35%. The maximal pulmonary arteriovenous shunt encountered in the post hemorrhagic shock patients at 36 hours averaged 20± 8% and was accompanied by high cardiac indices (average 5.1± 1.3L/M^2/min) but no significant rise of pulmonary arterial pressure or peak inspiratory pressure (PIP). Severe pulmonary dysfunction subsequently occurred only in those patients who later became septic. The studies on the septic patients were divided according to the magnitude of the cardiac indices (the high indices averaged 4.8 ±1.6L/M^2/min) and the low indices averaged 1.9 ±1.0L/M^2/min. In the former, the average maximal shunt of 30± 6% was sustained for 4 or more days, accompanied by an elevation of PIP to 36 ± 6 cm H_2O and by Pa pressure of 28± 5 mm Hg. The patients in low output septic shock usually had an associated bronchopneumonia and had an average venous admixture of 34± 8% and PIP values of 41± 8 cm.H_2O. The mean Pa pressure in this group was 29± 6 mm Hg.

13. The effect of adrenocorticosteroid pretreatment on kinin system and coagulation response to septic shock in the baboon. C. M. Herman, G. Oshima, and E. G. Erdös. J. Lab. Clin. Med. 84: 731-739, 1974.

Baboons were subjected to lethal Escherichia coli septicemic shock, by injecting live organism with one group receiving pretreatment with 30 mg. per kilogram of methylprednisolone and the other group serving as untreated control animals. There was an early development of disseminated intravascular coagulation and kinin activation in both groups, with progressive cardiovascular collapse and death in all animals. The kinin precursor protein kininogen decreased to close to zero level. The difference between steroid-treated and nontreated groups was that plasma kallikrein levels desclined significantly in the non-treated animals. Under the conditions of the study, no other effects of corticosteroid treatment of septic shock were observed.

14. Effect of Bacterial Endotoxins on Carbohydrate Metabolism of Rabbits. Ernest Kun and C. Phillip Miller. Proc. Soc. Exptl. Biol. Med. 67: 221-225, 1948.

The intravenous injection of meningococcal or Salmonella endotoxin into rabbits produced increase in blood glucose, lactic acid and inorganic phosphorus. This was followed by hypoglycemia which could be observed

before the death of the animal. Liver and muscle glycogen decreased while lactic acid content of the tissues increased. The pyruvic acid content of blood and tissues showed a significant decrease. Succinic dehydrogenase in both muscle and liver was markedly inhibited. Cytochrome oxidase activity was not affected.

15. Direct Effects of Endotoxin on Canine Gastric Mucosal Permeability and Morphology. Laurence Y. Cheung, M.D., Laurence W. Stephenson, M.D., Frank G. Moody, M.D. Michael J. Torma, M.D., and Charlotte Zalewsky, M.S. J. Surg. Res. 18: 417-425, 1975.

The effects of endotoxin on gastric mucosal permeability and morphology were studied by intra-arterial infusion of sublethal doses of endotoxin into a single artery perfusing an exteriorized segment of canine stomach. Endotoxin infusion produced a profound change in mucosal appearance from bright, uniform red to mottled, pale-white discoloration when exposed to acid or mannitol. Gross erosions occurred in four of 13 mucosae bathed with 0.15 N HCl within 1 hr of infusion of endotoxin in the absence of arterial hypotension. Histological changes seen in most experiments include release of mucus from surface epithelial cells and elevation of the epithelium from the basement membrane. In more advanced lesions, severe injury extended into the gastric glands and surrounding connective tissue with cellular necrosis. In spite of gross and microscopic gastric mucosal injury, no significant change was seen in hydrogen ion back diffusion or sodium efflux. These observations suggest that gastric mucosal injuries can occur in endotoxemia without systemic arterial hypotension and that anatomical mucosal injuries are not associated with the destruction of the hydrogen-sodium permeability barrier.

16. Membrane Transport: Its Relation to Cellular Metabolic Rates. J. Elbrink and I. Bihler. Science 188: 1177-1184, 1975.

The regulation of sugar transport in several animal tissues is correlated with the metabolic requirements of each tissue. As a general rule, in tissues where glucose utilization is stable, free intracellular glucose is present and the transport system has more than sufficient capacity to supply the required substrate. In this category are the mature mammalian erythrocyte and the lens of the eye. Transport is also not rate limiting in the liver although its metabolic rate is variable; this may be related to the very large capacity of its transport system, suited to rapid release as well as rapid uptake of glucose. As for the brain although the rate of glucose metabolism in this organ appears to be variable under certain conditions, whether or not the transport step itself is also regulated has not yet been determined.

In tissues where glucose utilization is variable, its penetration across the cell membrane is rate limiting providing an additional means of controlling metabolism through a number of feedback systems. This is the case in various types of muscle, in adiopose tissue, and perhaps in some other tissues. Cellular activities which result in greater enery consumption, and other changes in the tissue's pattern of metabolism, modulate sugar transport in a manner consistent with the concomitant changes in its metabolism; this has been called activity or demand regulation. The effect of insulin in increasing sugar transport in coordination with its stimulatory effect on the synthesis on energy reserves is an example of storage of supply regulations.

17. Shock Lung: Fact or Fancy? Arnold J. Rosen, M.D. Surg. Clin. N. Amer. 55:613-626, 1975.

Shock lung can be considered a relatively new pathologic syndrome. Its rapidly increasing incidence is a tribute to advanced sophistication in the salvage of severely traumatized patients and in those undergoing major surgery who would not have survived 25 years ago. No single factor can be credited as the sole precipitator of this syndrome. Alone, many of the factors may be insignificant; but combined they are often synergistic and end in a respiratory death. Although all of the mechanisms and interrelationships are not known for every case, early recognition of the specific contributing etiologies aid in both the prevention and, when that fails, in the treatment of shock lung. Today, by careful precise diagnostic monitoring, many cases of post-traumatic pulmonary insufficiency, i.e., shock lung, can be treated with resultant cure. The term shock lung is valuable only in alerting the physician to the fact that the patient is in "big troubie." The physician must then try to sort out all of the possible factors and treat each accordingly.

We might compare the end result of shock lung to the end stage of renal disease. The fact is that they are both nonspecific responses of an end organ to many different and interrelated etiologies. To expect to define a single, all encompassing etiology is pure fancy.

18. The Cardiovascular Physiology of the Critically Ill Patient. Matthew N. Levy, M.D. Surg. Clin. N. Amer. 55: 483-499, 1975.

The most subtle and crucial problem in understanding the cardiovascular derangements which occur during acute emergencies involves the nature of the coupling between the heart and the vascular system. Most surgeons possess considerable information about the changes in the heart and in the heart and in the vascular system individually under such conditions. However, the principal difficulty is related to the manner in which the two major components of the cardiovascular system interact with one another.

This article will deal with the relationships between the heart and vascular system, concentrating on those interactions which take place during acute emergency situations. In order to develop the subject, a model of the cardiovascular system will be presented which will, at first, contain only the least number of essential components. Other components will then be added as needed so that the model will more closely approach the complexity of the real cardiovascular system.

19. Role of Anaerobic Metabolism in the Preservation of Functional Capacity and Structure of Anoxic Myocardium. Arnold M. Weissler, Fred A. Kruger, Nobuhisa Baba, Dante G. Scarpelli, Richard F. Leighton, and Judith K. Gallimore. J. Clin. Invest. 47: 403-416, 1968.

Employing an isolated perfused rat heart preparation, we investigated the contribution of anaerobic metabolic energy to the performance, recoverability, and ultrastructure of the heart perfused at 32°C in 5% albumin in Krebs-Ringer Bicarbonate solution. During exposure to anoxia for 30 min, inclusion in the perfusate of the anaerobic substance, glucose, resulted in marked improvement in electrical and mechanical performance of the heart and in enhanced recovery during the subsequent period of reoxygenation. Lactate production was fivefold greater in the glucose-supported anoxic heart than in the anoxic heart without glucose. Electron microscope sections of the

hearts exposed to anoxia in the absence of glucose revealed alterations in mitochrondrial morphology and dilatation of the longitudinal tubules. These morphologic changes during anoxia were averted by inclusion of glucose in the perfusion fluid. The data are consistent with the hypothesis that anerobic energy generation plays a significant role in preserving myocardial function and structure and in promoting recoverability of the anoxic mammalian heart.

20. Pulmonary Edema in Patients with Sepsis. R. J. Finley, M.D., R. L. Holliday, M.D., F.R.C.S.(C), M. Lefcoe, M.D., and J. H. Duff, M.D., F.R.C.S.(C), F.A.C.S. Surg. Gynec. Obstet. 140:851-857. 1975.

Fiftenn critically ill patients with sepsis, 12 of whom had significant pulmonary dysfunction develop, were investigated with regard to changes in pulmonary capillary pressure, in serum oncotic pressure and on roentgenograms of the chest. It could not be shown that the pulmonary edema, which is a major characteristic of the septic lung lesion, was due to changes only in oncotic and hydrostatic pressures. Nor was there evidence that increased capillary permeability was the sole explanation of the edema. A significant relationship was found which consisted of increasing severity of the lung lesion, decreasing serum oncotic pressure and increasing pulmonary capillary pressure. When patients with sepsis require resuscitation with fluids, the administration of moderate amounts of albumin along with monitoring of pulmonary capillary pressure appears to be a rational approach to therapy.

21. Myocardial performance during hemorrhagic shock in the pancreatectomized dog. Bernell Coleman, John E. Kallal, Larry P. Feigen, and Vincent V. Glaviano. Amer. J. Physiol. 228(5): 1462-1468. 1975.

Myocardial performance was evaluated in nine pancreatectomized and 12 nonpancreatectomized dogs by measuring left ventricular pressure (LVP), maximal dP/dt (max dP/dt), left ventricular end-diastolic pressure (LVEDP), pulmonary arterial pressure (PAP), aortic pressure(AoP), and lead II of the electrocardiogram during standardized hemorrhagic shock. Cardiac output (CO) and hematocrit were determined before hemorrhage, after 4 h of oligemia, and when postinfusion mean blood pressure declined to 60 mmHg. Left ventricular function curves were obtained, by varying preload, in control dogs and 2 h after reinfusion of the shed blood in those dogs subjected to shock. Both groups of dogs showed identical responses to the shock procedure. In the immediate postinfusion period, LVP, max dP/dt, LVEDP, and mean blood pressure returned to near-control values, while PAP was significantly elevated. The post-infusion decline (after 60-90 min) in AoP was accompanied by a similar reduction in LVEDP. Left ventricular performance in hemorrhagic shock did not differ significantly from that seen in control dogs. In addition, there was no electrocardiographic indication of myocardial ischemia. The data indicate that terminal hemorrhagic shock need not be accompanied by myocardial depression whether or not the pancreas is intact.

22. Fibrinogen levels after inflammation or endotoxin in normal and hypophysectomized rats. Scott H. Goodnight, Samuel I. Rapaport, and Ariella Zivelin. Am. J. Physiol. 228(5): 1575-1579. 1975.

The hypothesis that pituitary hormones are required for increased fibrinogen synthesis after inflammation or endotoxin was tested by measuring plasma fibrinogen concentration after inflammation or endotoxin in normal and hypophysectomized rats. Animals were divided into groups receiving no exogenous adrenal steroids, low-dose adrenal steroids, or high-dose adrenal steroids. Hypophysectomy failed to prevent fibrinogen levels from rising after intra-

muscular turpentine (mean 240 mg/100 ml prior to and 556/mg 24 h after turpentine). Steroids did not suppress this rise. Endotoxin, 5 ug/100 g, caused a marked rise in fibrinogen in normal rats at 24 h (mean 296 mg/100 ml before endotoxin and 554 mg/100 ml after endotoxin). This dose of endotoxin killed hypophysectomized rats within 12 h. However, if hypophysectomized rats were protected with high-dose adrenal steroids, then 5 ug of endotoxin per 100 g caused the same fibrinogen rise as in normal rats (mean 299 mg/100 ml before endotoxin and 587 mg/100 ml after endotoxin). Apparently, pituitary hormones are not necessary for increased fibrinogen synthesis after either inflammation or endotoxin in the rat.

23. Direct Influence of Endotoxin on Cellular Respiration. Alden H. Harken, M.D., Richard S. Lillo, B.S., and Howard V. Hufnagel, B.S. Surg. Gynec. Obstet. 140: 858-860. 1975.

Hepatocyte oxygen consumption was evaluated in vitro in 70 rabbits. In selected instances, Escherichia coli endotoxin was added to a chamber containing either rabbit hepatocytes or hepatocyte homogenates. Endotoxin directly depressed the respiration of intact rabbit hepatocytes. Endotoxin also decreased the oxygen consumption of hepatocyte homogenates. The intact cell membrane is not an effective barrier to the deleterious effect of endotoxin. A patient in a state of endotoxic shock, in addition to having a hemodynamic derangement, probably has circulating toxins that directly render cellular oxidative phosphorylation less efficient.

24. Dilutional Re-Expansion with Crystalloid After Massive Hemorrhage: Saline Versus Balanced Electrolyte Solution for Maintenance of Normal Blood Volume and Arterial pH. Arturo L. Cervera, Ph.D., P.E., and Gerald Moss, M.D., F.A.C.S. J. Trauma 15: 498-503, 1975.

When administered in sufficient amounts, normal saline and Lactated Ringer's Solution are equally effective in maintaining adequate circulatory volumes despite severe blood loss and resltant hypoproteinemia. Arterial pH is maintained within normal limits when either solution is used for resuscitation provided the circulatory volume has been re-expanded to adequate levels for good tissue perfusion and support of aerobic metabolism. The pH of the infused solutions has no effect on blood pH under these circumstances.

Fourteen splenectomized dogs were subjected to continuous hemorrhage and simultaneous replacement with either normal saline or Lactated Ringer's Solution. The cumulative replacement volume ratio necessary for equilibration after 61% RBC depletion was 7:1 crystalloid to the whole "undiluted" blood shed, in both groups. Indicators of pulmonary-circulatory physiology remained stable within normal limits.

Arterial pH did not exhibit significant changes from normal values after resuscitation with NS or LRS. The group infused with LRS exhibited no change in arterial pH, 7.40± .07 initial and 7.40 ± .09 final; in the group with NS replacement a slight decrease from control was noted, 7.40 ± .07 initial and 7.36 ± .06 final. These differences, however, are not statistically significant.

Of the 14 subjects, 13 were long-term survivors. The one death was associated with a technical mishap shortly after completion of the experiment.

Because banked blood imposes a "net" alkaline metabolic load (sodium citrate), patients expected to be transfused with large volumes of stored blood might

be better resuscitated with normal saline than with Ringer's Lactate Solution, to minimize or avert the otherwise resultant metabolic alkalosis.

25. Insulin Resistance in Experimental Shock. Irshad H. Chaudry, Ph.D., Mohammed M. Sayeed, Ph.D., Arthur E. Baue, M.D. Arch. Surg/Vol. 109, Sept., 1974.

Previously adrenalectomized (ADX) rats were bled to a mean arterial pressure of 40 mm Hg and maintained for 1 1/2 hours. Basal glucose uptake by isolated soleus muscle from ADX normal rats and ADX rats subjected to shock ("shock" muscles) increased with the increase in medium glucose concentration and uptake was similar in both groups of muscles. This indicates that shock per se did not produce any alterations in the basal glucose carrier mechanism. Insulin (0.1 unit/ml) increased uptake in ADX control but not in ADX shock muscles. Maximal stimulation of glucose uptake in shock muscles was observed at an insulin concentration of 0.2 unit/ml insulin. These experiments provide the first direct evidence that the responsiveness of tissues to insulin is altered during shock. This alteration could not be due to increased steroid or epinephrine output during shock.

26. Effects of Vasoactive Agents on Intestinal Oxygen Consumption and Blood Flow in Dogs. Wieslaw Pawlik, A. P. Shepherd, and Eugene D. Jacobson. J. Clin. Invest. 56:484-489, 1975.

A comparison study of several vasoconstrictor and vasodilator agents was conducted measuring changes in intestinal blood flow and oxygen consumption during 10-min periods of intra-arterial infusion. Blood flow was measured in a branch of the superior mesenteric artery of anesthetized dogs with an electromagnetic blood flow meter, and the arteriovenous oxygen content difference across the gut segment was determined photometrically. Vasopressin (4×10^{-3} and 7×10^{-4} U/kg-min) diminished blood flow 60 and 28% and reduced oxygen consumption 54 and 22%, respectively (all $P<0.001$). In a dose which did not lower blood flow, vasopressin still caused a decline in oxygen consumption ($P<0.01$). Epinephrine (5×10^{-2} µg/kg-min) decreased blood flow 19% ($P<0.001$) but did not reduce oxygen consumption. After β-adrenergic blockade, however, the same dose of epinephrine decreased blood flow 41% and oxygen consumption 33% (both $P<0.001$). Responses to angiotensin II, calcium chloride, and prostaglandin 2α resembled effects of vasopressin rather than those of epinephrine, namely decreased blood flow and decreased oxygen consumption. The vasodilator agents, prostaglandin E_1, isoproterenol, and histamine, increased ($P<0.001$) both blood flow (130, 80, and 98%, respectively) and oxygen consumption (98, 64, and 70%, respectively). Vasopressin, angiotensin II, calcium chloride, and prostaglandin $F_{2\alpha}$ appear to contract arteriolar and precapillary sphincteric smooth muscle indiscriminately to evoke both intestinal ischemia and hypoxia. Epinephrine is the exceptional constrictor in this case, producing diminished blood flow without a reduction in oxygen uptake.

27. Human Skeletal Muscle Energy Metabolism during and after Complete Tourniquet Ischemia. Hengo Haljamäe, M.D., Elling Enger, M.D. Anns. Surg. 182:9-14, 1975.

The extent of cellular metabolic deterioration and its reversibility was studied on human skeletal muscle needle biopsies during operations in bloodless field. The tissue levels of high energy phosphates and glycolytic

metabolites were analyzed after various times of tourniquet ischemia and compared to contralateral control extremity levels. In the ischemic extremity the phosphocreatine (CrP) levels decreased by 40% within 30-60 min and after 60-90 min a 60% reduction was found. No significant ATP changes occurred. Lactate levels increased by 225% after 30-60 min and by 300% after 60-90 min. The glucose and G-6-P levels increased slightly and indicated glycogenolysis. The rate of the metabolic changes decreased with ischemia time. In the control leg no significant metabolic changes could be seen. After the release of the tourniquet there was a rapid restoration of the phosphagen content and clearance of lactate in the ischemic leg. Near control levels of these substances were seen already after 5 min. The present results show that clinical tourniquet ischemia of up to 90 min duration produces less pronounced metabolic alterations than those seen in working muscle.

28. Sepsis and Hypercalcemia. Philip E. Cryer, M.D., and John Kissane, M.D. Am. J. Med. 59: 79-88, 1975.

    Stenographic reports edited by Philip E. Cryer, M.D. and John Kissane, M.D. of weekly clinicopathologic conferences held in Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of Washington University School of Medicine.

29. Influence of Increased Circulating Levels of Splanchnic Lysosomal Enzymes on the Response to Myocardial Ischemia. James A. Spath, Jr., Ph.D., Elise A. Reed, B.A., and Allan M. Lefer, Ph.D. Anns. Surg. 181: 813-818, 1975.

    The ability of increased circulating activities of lysosomal hydrolases to disrupt myocardial cellular membranes was studies in anesthetized cats. Increased activities of lysosomal hydrolases were achieved by splanchnic artery occlusion (SAO) shock or by infusion of liver extract (LE). Myocardial ischemia (MI) was produced by ligation of the left coronary artery. Coronary artery ligation resulted in sustained S-T segment elevation associated with significant increases in plasma creatine phosphokinase (CPK) activity within 5 hours. Combination of SAO or LE infusion did not modify the increase in either the plasma CPK activity or the S-T segment following MI. However, SAO shock or infusion of LE increased CPK loss from normal and ischemic myocardium, the loss being greater when MI was combined with infusion of LE or SAO shock. Similarly, MI plus SAO shock increased the loss of the lysosomal protease cathepsin D from normal and ischemic myocardial tissue. Moreover, cats subjected to MI and given LE exhibited increased mortality and decreased clearance of infused lysosomal hydrolases. These results indicate that conditions affecting increased plasma levels of hydrolases promote increased disruption of normal and ischemic myocardial tissue. These findings are consistent with the concept that hydrolases originating in the splanchnic viscera during shock play a role in enhancing damage to normal and ischemic myocardial tissue following coronary artery occlusion.

30. Pathologic Pulmonary Changes in Hemorrhagic Shock. Julius W. Garvey, M.D., Jack W. C. Hagstrom, M.D., Frank J. Veith, M.D. Anns. Surg. 181: 870-875, 1975.

    Fifty-seven dogs were subjected to hemorrhagic hypotension by a variety of protocols. Histologic pulmonary changes were studied using the light microscope. Of these 57 dogs, 21 had no demonstrable lesions, 8 had

minimal changes, and 28 had moderate or severe lesions, all of a focal nature. No correlation was found between the presence of lesions and mean systemic arterial pressure during shock, the duration of the hemorrhagic period, the fate of the animal, preoperative hematocrits and blood volumes, mean postreinfusion arterial pressure, whether the animals were mongrels or purebred beagles. Whether they were awake or sedated, whether they breathed spontaneously or were artificially ventilated, whether they had undergone previous splenectomy or not, whether hilar stripping was performed or not, and finally, whether blood was reinfused after hemorrhage or not. Thus we conclude that multiple factors may exert a harmful effect on the lung in hemorrhagic shock, and that shock probably makes the lungs more vulnerable to other injurious agents rather than there being one single pathogenetic mechanism for the pulmonary damage. The term "adult respiratory distress syndrome" rather than "shock lung" is best used for the human clinical entity since it implies a complex etiology rather than a discrete pulmonary lesion produced by a single pathogenetic mechanism.

31. Glucocorticoid and Antibiotic Effect on Experimental Gram-Negative Bacteremic Shock. Mary Pitcairn, James Schuler, M.D., Peter R. Erve, Ph.D., Steven Holtzman, M.D., William Schumer, M.D. Arch. Surg. 110: 1012-1015, 1975.

This study was designed to answer the three following questions: (1) Are glucocorticoids as protective in Gram-negative bacteremic shock as they are in endotoxic shock? (2) Is there any difference in efficacy between a bacteriostatic and a bactericidal antibiotic in bacteremic shock? (3) Does the combination of glucocorticoid with antibiotic potentiate the individual protective effects of both? Bacteremia was induced in male Sprague-Dawley rats by a single intravenous injection of viable Escherichia coli. The results showed that dexamethasone sodium phosphate alone afforded significant protection against Gram-negative bacteremic shock up to eight hours after challenge. The choice of a bactericidal vs a bacteriostatic antibiotic did not influence the survival rates in this study. The survival rate was maximal when dexamethasone was used with both ampicillin sodium and gentamicin sulfate.

32. Metabolic Effects of Amino Acid vs Dextrose Infusion in Surgical Patients. Joel B. Freeman, M.D., Lewis D. Stegink, Ph.D., Paul D. Meyer, M.D., Robert G. Thompson, M.D., Lawrence DenBesten, M.D. Arch. Surg. 110: 916-921, 1975.

We tested the hypothesis that during infusion of amino acids without dextrose, there is less insulin stimulation, which, in turn, permits lipolysis. The results suggest that dextrose infusion stimulates insulin and inhibits lipolysis. During administration of crystalline amino acids without dextrose, nitrogen balance improved substantially from control values obtained during dextrose infusion, while the level of serum-free fatty acids and ketone bodies rose and that of serum immunoreactive insulin fell. Infusion of amino acids at 1.7 gm/kg appeared slightly more efficient than infusion at 1.0 gm/kg and did not stimulate insulin or inhibit lipolsis. Protein sharing may be useful in certain specific clinical situations. However, the results must be interpreted cautiously, primarily because it is difficult to establish the relationship between improvement in nitrogen balance and the derived clinical benefit. Absolute proof of the efficacy of this technique awaits further studies using indexes that more accurately measure protein synthesis.

33. Effects of Glucose, Insulin and Potassium Infusion on Tissue Metabolic Changes within First Hour of Myocardial Infarction in the Baboon. L. H. Opie, M.D., K. Bruyneel, M.D., and Patricia Owen, B.Sc. Circ. 52: 49-59, 1975.

The effects of infusions of glucose, insulin and potassium (GIK) on the heart tissue metabolic changes found in adult baboons 60 min after coronary artery ligation were studied. Biopsies taken from 11 baboons without coronary artery ligation gave control values. A second group of 46 baboons had coronary artery ligation. A third group of 17 baboons received an infusion of KCl after coronary artery ligation. A fourth group of 26 baboons received infusions of GIK. Coronary artery ligation resulted in the expected fall of ATP, creatine phosphate, glycogen, tissue (K^+/Na^+) ratio,and tissue pH, and rise of inorganic phosphate, lactare, lactare/ pyruvate ratio and α-glycerophosphate in the infarction zones. Compared with ligation, additional infusions of GIK approximately doubled the contents of creatine phosphate and glycogen in the infarct zones, increased the content of ATP in the central infarct zone, and decreased the content of inorganic phosphate in the peripheral infarct zone. Other GIK effects were that the tissue (K^+/Na^+) ratio rose in the peripheral infarct zone, and the content of both glycogen and lactate rose in the peri-infarct and non-ischemic zones; the pH of tissue homogenates did not decrease. KCl infusions had few effects compared with the ligation group. GIK infusions exerted a beneficial effect when compared with infusions of KCl in that tissue creatine phosphate rose in the peripheral infarct and nonischemic zones; the tissue K^+/Na^+ Ratio rose in the peripheral infarct, peri-infarct, and nonischemic zones; and the lactate/pyruvate ratio fell in the infarct zone. It is proposed that GIK counteracted early tissue metabolic deterioration in the infarcting baboon heart.

34. Effects of Exogenous cyclic adenosine monophosphate in hemorrhagic shock. M. L. MacRae, B.Sc., C. J. Chiu, M.D., Ph.D., and E. J. Hinchey, M.D. Surg. 78: 254-260.

Hemorrhagic shock produces potentially damaging alterations in the metabolism of cyclic adenosine 3', 5' - monophosphate (cAMP), which is an intracellular second messenger for many hormones. The hypothesis that the administration of exogenous cAMP might have salutary effects on cardiovascular hemodynamics in shock was tested in canine experiments. Intravenous bolus injection of dibutyryl cAMP (2 mg. per kilogram) produced hyperglycemia, but no changes occurred in heart rate, arterial pressure, cardiac output, or in the first derivative of left ventricular pressure (dp/dt). The findings were similar in conscious and anesthetized (Nembuta) normotensive dogs, in dogs after 3 hours of shock (at blood pressure of 40 mm. Hg) and after the reinfusion of shed blood. The only hemodynamic change noted was a transient hypotension upon injection of massive doses of dibutyryl-(db-) cAMP or cAMP (>10 mg. per kilogram). The implication of these findings in light of earlier reported hemodynamic effects of cAMP is discussed.

35. Diastolic Compliance of the Left Ventricle in Man. William H. Gaasch, M.D., FACC, Miguel A. Quinones, M.D., Efrain Waisser, M.D., Hans G. Thiel, M.D., James K. Alexander, M.D., FACC. Am. J. Cardiol. 36: 193-201, 1975.

Two coordinates of left ventricular end-diastolic pressure (P) and volume (V) were provided by the infusion of angiotensin in 22 patients. The slope

(k) of the In P-V relation, coupled with knowledge of the operating (end-diastolic) pressure allows determination of end-diastolic volume compliance (dV/VdP). Estimates of end-diastolic compliance from a single coordinate of pressure and volume compared well (r = 0.90) with the two coordinate method, whereas values for specific compliance ($\Delta V/V_1 \Delta P$) appeared to be misleading in cases of idiopathic hypertrophic subaortic stenosis and congestive cardiomyopathy. Since volume compliance is determined in part by the operating pressure, compliance may be reduced in small, normal, or enlarged ventricles.

Left ventricular linear compliance was derived from volume compliance and was normalized for left ventricular wall thickness. The product of linear compliance and end-diastolic stress provides an index of myocardial strain, termed "muscle fiber stretch," which may be related to systolic performance and thus allow comparison of length-performance relations in ventricles with normal and abnormal compliance.

36. Pulmonary gas exchange in the critically ill patient. John B. West, M.D. Ph.D. Crit. Care Med. 2: 171-180, 1975.

A new method for determining the distribution of ventilation-perfusion ratios in critically ill patients in the intensive care setting is described. The method is based on the infusion of a mixture of inert gases into the venous circulation with a subsequent measurement of the gas concentrations in arterial blood and mixed expired gas by gas chromatography. Young normal subjects show very narrow distributions of ventilation and blood flow with respect to ventilation-perfusion ratio. These distributions broaden with increasing age. Oxygen breathing causes the development of shunts in both normal and abnormal lungs, particularly in patients with lung disease. The mechanism of this is discussed. Measurements of shunt after 100% oxygen generally result in overestimates. In some abnormal lungs, positive end-expiratory pressure decreases the amount of shunt and also results in increased amounts of ventilation going to units with very high ventilation-perfusion ratios. Preliminary results suggest that the new test may be of diagnostic value in some settings; eg, detecting pulmonary embolism in critically ill patients.

37. Correlation of positive end-expiratory pressure with cardiovascular performance. Samuel R. Powers, Jr., Robert E. Dutton, M.D. Crit. Care Med. 3: 64-68, 1975.

This report describes the results of a series of investigations carried out on patients subjected to various levels of PEEP in the Trauma Unit of the Albany Medical Center Hospital.

38. Rational ventilator modes for respiratory failure. Henrik H. Bendixen, M.D. Crit. Care Med. 2: 225-227, 1975.

The general guidelines outlined in this presentation will contribute to more effective use of the respirator in the majority of patients. Although the proper use of mechanical ventilation is o utmost importance in the treatment of acute respiratory failure, there is no magic in the respirator. It simply happens to be one of the most important tools when respiratory failure occurs or is imminent. However, it is only a tool. The underlying disease must be treated successfully.

39. Monitoring respiratory function. John J. Osborn, M.D. Crit. Care. Med.2: 217-220, 1974.

The status of patients on respirators can change very suddely; therefore, continuous airway monitoring which can provide data on the immediate status of respiratory function can be life-saving as well as contribute to the making of sound clinical decisions.

A system for continuous monitoring and analysis of respiratory gas, pressure, and flow is presented.

40. Pulmonary microcirculation. Cellular pathophysiology in acute respiratory failure. James W. Wilson, Ph.D., M.D. Crit. Care. Med. 2: 186-199, 1974.

Pulmonary failure associated with shock from myocardial infarction, sepsis, trauma, and numerous other situations can be related to a cellular metabolic problem. Perhaps the most important emerging concept in cellular physiology and microcirculatory research today is that the lung exhibits a uniform response to injury, whether mediated via the vasculature or the airways. The serious and often fatal nature of syndromes and diseases affecting the lung requires that every physician treating patients familiarize himself with the cellular morphologic and physiologic data presently available. An awareness of the hazards of oxygen, a knowledge of sophisticated pharmacologic therapy, a high index of suspicion for developing acute respiratory failure, and good clinical judgment tempered by experience may allow the salvage of a higher percentage of patients with pulmonary failure.

41. Transcapillary Fluid Movements in Sympathectomized Intestine and Skin During Hemorrhagic Hypotension. Johannes Järhult and Per-Olof Grände. Acta Physiol. Scad. 94: 29-35, 1975.

Net transcapillary fluid exchange in skin tissue (paw) and small intestine was observed during a 90 min period of hemorrhagic hypotension at 50 mm Hg in the cat. Reflew fluid transfer was prevented by regional sympathectomy and α-adrenergic blockade. Early in hemorrhage, fluid absorption from the extravascular space occurred in both tissues, apparently caused by osmosis. The process was thus co-ordinated in time with a positive arterio-venous osmolar difference, in turn caused by a marked arterial hyperosmolality. Experimental arterial hyperosmolality of similar magnitude, created by i.v. infusion of hypertonic glucose in non-bled animals, led to transcapillary fluid absorption in both intestine and skin and at rates similar to those in bleeding. Regional hypotension per se caused no fluid absorption. Later in hemorrhage (>30 min), plasma fluid moved into the extravascular space both in skin and intestine, apparently due to a gradual increase of capillary hydrostatic pressure. It is concluded that the arterial hyperosmolality during bleeding can cause transcapillary fluid absorption in intestinal and skin tissues, as previously shown for skeletal muscle (Järhult 1973). The hemodynamic significance of this process for plasma volume regulation in hemorrhage is, however, much greater in skeletal muscle than in intestine and skin, mainly due to the much larger total mass of the muscle tissue.

42. Multiple, Progressive, or Sequential Systems Failure. Arthur E. Baue, M.D. Arch. Surg. 110:779-781, 1975.

As the care of injured patients has evolved and improved, various organ systems have in turn been the limiting factor affecting recovery after a severe injury or major operation. The major wars have provided larger experience and more concentrated documentation of what was happening simultaneously in civilian hospitals to patients traumatized by injury or operation. In the 1930s and during the early part of World War II, the major organ system that limited survival after injury was the cardiovascular apparatus (shock), even when that system was previously normal. By the end of World War II, the kidney emerged as the most prevalent limiting organ system, and during the Korean War, acute renal failure after injury or after operation was still a major roadblock to recovery for many. Then in the 1960s the lung became the limiting organ. Lung problems were described as shock lung, pump lung, and finally by the more general term, posttraumatic pulmonary insufficiency, just as renal problems were called posttraumatic renal insufficiency during the Korean conflict. The reports of the Surgical Research Team in Korea do not mention the lung as a problem, whereas during the Vietnam War, the incidence of renal failure had become low but pulmonary difficulties were common.

43. The Benefits of Corticosteroids in Endotoxic Shock. Richard Prager, M.D., Marvin M. Kirsh, M.D., Ernest Dunn, M.D., Ronald Nishiyama, M.D., John Straker, B.S., Robert Lee, B.S., and Herbert Sloan,M.D. Anns. Thoracic. 19:142-152, 1975.

The experiments reported here were undertaken to study the effects of pharmacological doses of corticosteroids administered alone or in conjunction with prolonged (12-hour) assisted circulation in 22 dogs subjected to LD_{50-60} Escherichia coli endotoxin. The most striking findings were lengthened survival time, higher cardiac output, decreased fluid requirement, and minimal evidence of pulmonary congestion or injury in the animals treated with steroids only. Unexplained mesenteric infarction prematurely terminated the experiments in animals undergoing assisted circulation.

The benefits of corticosteroids in experimentally induced endotoxic shock are clearly demonstrated in these experiments. Further studies are needed to clarify the supportive role of assisted circulation in endotoxic shock and to determine any possible advantage of hypothermia over normothermia during its course.

44. Intramyocardial Pressure: Effect of Preload on Transmural Distribution of Systolic Coronary Blood Flow. Joseph P. Archie, Jr., Ph.D., M.D. The Amer. Journal of Cardiology 35:904-911, 1975.

Impairment of systolic coronary blood flow (CBF) may be mediated by intramyocardial pressure (P_{IM}). However, the effect of systole on the magnitude and transmural distribution of coronary blood flow has not been investigated. The purpose of this study was to measure this effect, and indirectly, intramyocardial pressure. Coronary perfusion pressure minus intramyocardial pressure equals resistance times coronary blood flow. These data show that intramyocardial pressure shuts off systolic coronary blood flow across the entire left ventricular wall at low levels of preload, and at high levels of preload determines a gradient of decreasing systolic coronary blood flow from the subepicardium to zero in the subendocardial layers. This finding suggests that a dilated or failing left ventricle receives systolic flow to the outer myocardial layers, whereas at low preload levels myocardial perfusion occurs entirely during diastole.

45. Effects of Nitroglycerin on Transmural Myocardial Blood Flow in the Unanesthetized Dog. Robert J. Bache, Robert M. Ball, Frederick R. Cobb, Judith C. Rembert, and Joseph C. Greenfield, Jr. J. Clin Invest., 55: 1219-1228, 1975.

This study was designed to determine the effect of nitroglycerin upon transmural distribution of myocardial blood flow in the awake dog during normal conditions and in the presence of ischemia- induced coronary vasodilation Studies were performed in chronically prepared dogs with electromagnetic flowmeters and hydraulic occluders on the left circumflex coronary artery. Regional myocardial blood flow was estimated by using radionuclide-labeled microspheres, 7-10 μm in diameter, injected into the left atrium. During control conditions endocardial flow (0.86±SEM 0.05 ml/min per g) slightly exceeded epicardial flow (0.72±0.03 ml/min per g, $P<0.05$), and this distribution of flow was not significantly altered by nitroglycerin. After a 5-s coronary artery occlusion, reactive hyperemia occurred with excess inflow of arterial blood effecting 360±15% repayment of the blood flow debt incurred during occlusion. When arterial inflow was limited to the preocclusion rate during coronary vasodilation after a 5-s total coronary artery occlusion, flow to the subepicardial myocardium was increased at the expense of underperfusion of the subendocardial myocardium, and the delayed reactive hyperemia was markedly augmented (mean blood flow debt repayment = 775±105%, $P<0.01$). These data suggested that subendocardial underperfusion during the interval of coronary vasodilation in the presence of a flow-limiting proximal coronary artery stenosis caused continuing subendocardial ischemia which resulted in augmentation of the reactive hyperemic response. In this experimental model both the redistribution of myocardial blood flow which occurred during an interval of restricted arterial inflow after a 5-s coronary artery occlusion and augmentation of the subsequent reactive hyperemic response were returned toward normal by nitroglycerin. This effect of nitroglycerin may have resulted, at least in part, from its ability to vasodilate the penetrating arteries which deliver blood from the epicardial surface to the subendocardium.

46. Effect of histamine on microvasculature of isolated dog gracilis muscle. J. E. McNamee and F. S. Grodins. Am. J. of Phys. 229:119-125, 1975.

McNamee, J. E., and F. S. Grodins. Effect of histamine on microvasculature of isolated dog gracilis muscle. Am. J. Physiol. 229(1): 119-125, 1975.- Isogravimetric capillary pressure (Pc_i), capillary filtration coefficient (CFC), and plasma protein concentration were measured before and during administration of histamine in an isolated, independently perfused canine gracillis muscle. Histamine produced an average decrease in Pc_i of 14.1 mmHg, an increase in CFC of 36-fold,and an increased rate of plasma protein escape of at least 24-fold. These results suggest that histamine reduces the reflection coefficient for protein at the capillary wall and are consistent with predictions of the theory of restricted diffusion assuming that 1-2.5% of available pores increase in radius from 40 to 240 Å.

47. The Significance of Altered Gluconeogenesis in Surgical Catabolism. Frank E. Gump, M.D., Calvin L. Long, Ph.D., John W. Geiger, A.B. and John M. Kinney, M.D. J. Trauma 15: 704-713, 1975.

Hepatic gluconeogenesis was investigated in five critically ill septic patients by examining the hepatic balances of glucose, urea, and 20 amino acids. Alanine uptake predominated and was consistently greater than values reported in normal subjects. The increased alanine uptake was associated with increased hepatic production of glucose and urea. Glucose production

in the five study patients was quite variable and calculations indicate that no more than 10% of the glucose released could be accounted for by the alanine taken up. However, the increased uptake of alanine suggests that gluconeogenesis was accelerated in these patients. The degree of incorporation of ^{14}C alanine into glucose was employed as a very direct means of quantitating gluconeogenesis in three additional septic patients. Exogenous glucose suppressed gluconeogenesis in normals but not in the injured, septic patients. The abnormal gluconeogenesis demonstrated in this study provides a link among hypermetabolism, glucose intolerance, and the increased urea excretion which are characteristically seen in critically ill surgical patients.

48. Secretory Regulation of Endocrine Pancreas: Cyclic AMP and Glucagon Secretion. Takayoshi Toyota, Shin-Ichiro Sato, Mikihiko Kudo, Kanji Abe, and Yoshio Goto. J. Clin. Endocrin. Metab. 41: 81-89, 1975.

Activation of adrenergic beta receptors has been found to stimulate insulin release in vitro that may be midiated through the augmentation of cyclic AMP in the beta cell. The activation of adrenergic alpha receptors in the beta cell inhibits the insulin release. The present studies have shown that isoproterenol (0.62 µg/ml) and sodium dibutyryl cyclic AMP (50 µg/ml) stimulate the insulin secretion and inhibit the glucagon secretion in the presence of 50 mg/100 ml glucose by the isolated pancreatic perfusion of the rat, while norepinephrine (0.5 µg/ml) inhibits the insulin secretion induced by 150 mg/100 ml glucose and stimulates the glucagon secretion. Theophylline (50 µg/ml) does not stimulate the insulin and the glucago secretion. When norepinephrine is added to theophylline, the output of glucagon does not occur. From these results it can be deduced that the pancreatic alpha cell function may be inhibited by elevation of intracellular cyclic AMP, in contrast to the beta cell function which is stimulated by an increment of cyclic AMP. (J Clin Endocrinol Metab 41: 81, 1975).

49. Effect of Insulin-Induced Hypoglycemia upon Plasma Renin Activity in Man. Stephen C. Lowder, Marshall G. Frazer, and Grant W. Liddle. J. Clin. Endocrin. Metab. 41: 97-105, 1975.

The effect of insulin-induced hypoglycemia upon plasma renin activity (PRA) was assessed in 4 normal volunteers, 4 adrenalectomized patients and 10 patients with various pituitary hormone deficiences. Significant increases in PRA were observed in all three groups. The PRA responses to hypoglycemia could be blocked by propranolol, and appeared to be potentiated by theophylline It is concluded that sympathetic reflex stimulation, not adrenal-dependent and not pituitary-dependent, is the major mechanism for this phenomenon in man and that this adrenergic effect may be mediated by cyclic AMP.
Plasma renin activity (PRA) has been reported to be increased following insulin-induced hypoglycemia in dogs (1), but the occurrence of this phenomenon in man has not been substantiated. The present report deals with measurements of plasma renin activity before and during insulin-induced hypoglycemia in a group of normal subjects and in two other groups of patients. The findings establish that hypoglycemia results in significant elevations in PRA and that this reponse persists following adrenalectomy and in the presence of hypopituitarism.

50. E. coli Endotoxin Shock in the Cat; Treatment with Indomethacin. J.R. Parratt & R.M. Sturgess. Br. J. Pharmac. 53: 485-488, 1975.

1. An earlier study had demonstrates that indomethacin, administered before E. coli endotoxin, abolished the initial pulmonary vasoconstriction and delayed the onset of the secondary shock phase that results from the in-

travenous injection of this agent in cats. The object of the present study was to determine whether indomethacin modified the shock phase when administered after endotoxin.
2. All the cats (whether or not they received indomethacin, 10 mg/kg) exhibited the characteristic features of the delayed shock phase that result from the administration of endotoxin (2 mg/kg). These included systemic hypotension, hypoglycaemia, reductions in arterial pH, cardiac output and systolic ejection time and an increase in arterial lactate. Five out of the ten animals given indomethacin survived 4 h compared with four out of twelve in the control (endotoxin alone) group.
3. These results do not support the suggestion that antipyretic-analgesic drugs like indomethacin may be of benefit when given during bacteraemic or septic shock. They do support the suggestion that the acute pulmonary changes (hypertension and decreased compliance) that occur in this species within a few minutes of endotoxin administration ultimately contribute to the severity of the shock phase.

51. Effects of cardiac lymphatic obstruction on coronary arteries. R. Randolph Bradham, M.D., Edward F. Parker, M.D., William B. Greene, B.S., and Gordon R. Hennigar, M.D. J. Thorac. Cardiovasc. Surg. 69: 876-879, 1975.

A study was undertaken to determine whether changes occurred in the coronary arteries of dogs after obstruction of the cardiac lymphatics. Other investigators have described changes in the walls of coronary arteries after cardiac lymphatic obstruction that caused compromise of the lumen. Adult mongrel dogs were subjected to an operation which occluded the cardiac lymphatics. Several days later, a second operation was done to remove specimens of the terminal branches of the coronary arteries. The specimens were studies by light and electron microscopy. There was no gross or microscopic evidence of altered morphology of the coronary arterial walls.

52. The use of methylprednisolone during cardiopulmonary bypass. Ronald H. Dietzman, M.D., Ph.D., John B. Lunseth, M.D., Ph.D., Bernard Goott, M.D. Ph.D., and Edward C. Berger, B.S. J. Thorac. Cardiovasc. Surg. 69: 870-873, 1975.

A study was designed to evaluate the hemodynamic effects of massive doses of methylprednisolone (30 mg. per kilogram) during cardiopulmonary bypass at normothermia and hypothermia. In 427 patients studies, significantly less vasoconstriction ($p < 0.01$) and improved perfusion flows ($p<0.0005$) were obtained at comparable pressure levels in the steroid-treated group (272 patients) compared with the control group (155 patients). Because of these measured parameters, methylprednisolone should be considered a valuable adjunct to improving tissue perfusion during cardiopulmonary bypass.

53. Myocardial ultrastructure and function during progressive early ischemia in the intact heart. Chaim Lichtig, M.D., and Harold Brooks, M.D. J. Thorac. Cardiovasc. Surg. 70: 309-315, 1975.

Regional contraction of ischemic anterior and normal lateral left ventricular myocardium was measured with isometric force gauges after 5, 10, 15, and 20 minutes of anterior descending coronary artery occlusion--each followed by 10 minutes of reperfusion. Multiple myocardial biopsies of both regions were taken at these same intervals and examined by electron microscopic techniques. Mean contraction of the ischemic area fell significantly in 15 to 30 seconds and returned to an average of 68, 51, 40, and

28 per cent, respectively, after 5, 10, 15, and 20 minutes of ischemia. Simultaneously, focal morphologic changes were detected after 5 and 10 minutes, were more clear and widespread at 15 minutes, and diffuse and unequivocal at 20 minutes, when return of local contraction was minimal. The changes of myocardial morphology in the ischemic area as seen by electron microscopy were: reduced content of glycogen granules and mitochodrial changes. The latter began to appear at 5 minutes and consisted of swelling, disruption of cristae, and reduction of matrix. This study indicates a qualitative correlation between ultrastructural changes in regionally ischemic myocardium and diminished regional function in the intact heart. At 5 and 10 minutes the mitochondrial changes were focal, requiring multiple samples, while at 15 and 20 minutes they became more widespread, making the occasional sample more representative.

54. Regulation of Postocclusive Hyperemia by Endogenously Synthesized Prostaglandins in the Dog Heart. R. Wayne Alexander, Kenneth M. Kent, John J. Pisano, Harry R. Keiser, and Theodore Cooper. J. Clin. Invest. 55: 1174-1181, 1975.

Experiments were performed to evaluate the role of prostaglandin synthesis in the regulation of coronary blood flow in dog hearts. The left main coronary was cannulated and flow measured both in otherwise intact animals and in canine heart-lung preparations. Prostaglandin E was measured by radioimmunoassay. Reactive hyperemia (flow after occlusion release) was induced by coronary occlusion for 10, 15 and 20 s and was 39±13 (mean±SEM), 66±21, and 82±24 ml, respectively. Indomethacin, an inhibitor of prostaglandin synthetase, reduced reactive hyperemia at 10, 15, and 20 s to 15±5, 33±11, and 47±17 ml respectively ($P<0.05$). Meclofenamate, a different prostaglandin synthetase inhibitor, gave similar results. In a second group of five dogs, prostaglandin production of the heart was examined in response to 20-s occlusions. There was a significant increase in prostaglandin production from a basal level of 18.6±4.9 rg/min to 35.3±5.8 ng/min after occlusion of the coronary artery of 20 s ($P<0.05$). After indomethacin, this increase in prostaglandin production was not observed and reactive hyperemia was significantly reduced. Thus, prostaglandin synthesis appears to be important in modulating canine coronary blood flow in response to brief periods of coronary occlusion.

55. Acute Fluid Replacement in the Therapy of Shock. Theodore I. Malinin, M.D., Robert Zeppa, M.D., William R. Drucker, M.D., Arthur B. Callahan, Ph.D. Stratton Intercontinental Medical Book Corporation, New York, N.Y., 1974.

This publication is comprised of a series of articles written by clinicians on the mechanism and therapy of shock.

56. Cellular glucose utilization during hemorrhagic shock in the pig. Peter D. Wright, M.D., F.R.C.S., and Kathleen Henderson. Surg. 78:322-333, 1975.

To clarify the changes in glucose homeostasis which occur following injury, pigs were subjected to hemorrhagic shock. During shock increased levels of free glucose occurred in red blood cells and muscle tissue, suggesting that inhibition of glucose phosphorylation was occurring. Simultaneously systemic plasma glucose levels were noted to be higher than portal plasma glucose levels while levels of free glucose within the liver fell, indicating that the liver was mobilizing glucose. Plasma insulin and phosphate levels were observed to rise throughout the experiment. From this study it was concluded that the hyperglycemia of injury in these animals

was caused by a combination of decreased cellular glucose utilization due to diminished phosphorylation and increased mobilization of glucose by the liver.

57. Platelet Physiology and Abnormalities of Platelet Function. Harvey J. Weiss, M.D. New Eng. J. Med. 293: 580-588, 1975.

As Deykin has indicated, these are palmy days for platelet researchers. In addition to their important role in hemostasis and thrombosis, platelets have been implicated in mediating various types of inflammatory and immunologic processes, vascular permeability, host-defense responses, and transplantation rejection reactions. Platelet reactivity may also be increased in diabetes, under conditions of stress, in Type II hyperlipoproteinemia, after cigarette smoking, and in some patients with manifest symptoms of ischemic heart disease. These findings suggest a possible link between platelets and conditions that predispose to the development of atherosclerosis and its complications.

Finally, platelets have also been implicated in mediating metastases in experimental tumors. On this note it may be appropriate to end this review.

58. Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. John J. Skillman, M.D., D. Sean Restall, M.D., and Edwin W. Salzman, M.D. Surg. 78: 291-303, 1975.

In a prospective randomized trial of 16 patients undergoing abdominal vascular reconstructive procedures, changes in plasma volume, serum oncotic pressure (πs), serum albumin and total protein concentration, alveolar to arterial oxygen tension differences (Aa_{DO_2}, $FI_{O_2}=1.0$), creatinine clearance, body weight, and fluid and sodium intake were examined. By random assignment patinets received either an albumin- or sodium-rich intraoperative fluid regimen. Pulmonary arteriovenous admixture was significantly less in the albumin group (n=7) than in the electrolyte group (n=9) on the first postoperative day. The change in Aa_{DO_2} correlated positively with the total sodium intake in the electrolyte group. Despite the larger fluid load and significantly greater gain of body weight, patinets in the electrolyte group had a postoperative plasma volume significantly lower than the preoperative value. Postoperative values of albumin concentration, circulating albumin mass and πs were significantly greater in the albumin group in comparison to the electrolyte group. Creatinine clearance values were not different between the two groups. The change in πs correlated significantly with sodium intake and circulating albumin mass. Pulmonary shunting and expansion of the extracellular fluid volume may be minimized without adverse effects on renal function by administration of fluids rich in albumin in preference to sodium.

59. Platelet Physiology and Abnormalities of Platelet Function. Harvey J. Weiss, M.D. (First of Two Parts) New Eng. J. Med. 293: 531-541, 1975.

There is impressive evidence that some aspects of platelet function share mechanisms in common with other secretory cells, that calcium-regulated contractile processes are involved, and that cyclic AMP may have a regulatory role. As in smooth muscle, platelet reactions are inhibited by cyclic AMP and stimulated by cyclic endoperoxide precursors of prostaglandins

E_2 and F_{2a}; a vesicular system that can regulate the cytoplasmic level of calcium, and hence regulate cellular activity, is present in platelet as in muscle. Whereas in muscle the sarcoplasmic reticulum serves as a calcium pump mechanism that regulates reversible cycles of contraction and relaxation, the activation of platelet contractile activity during secretion and clot retraction has usually been thought to be essentially irreversible. However, Cohen and de Vries have recently shown reversible contractile-relaxation activity in platelet-plasma clots studies under isometric conditions. Present evidence suggests that secretory-contractile processes in platelets are mediated by increases in the level of cytoplasmic calcium, and the possibility that these levels may be regulated by cyclic AMP seems worthy of further study. Finally, although the evidence to date strongly suggests that calcium-mediated contractile processes, perhaps regulated by cyclic AMP, have important roles in platelet function, the basic question how these are organized within the platelet to effect aggregation, release and contraction remains to be determined.

60. Lack of Clinical Usefulness of the Limulus Test in the Diagnosis of Endotoxemia. Ronald J. Elin, M.D., Ph.D., Richard A. Robinson, M.D., Arthur S. Levine, M.D., and Sheldon M. Wolff, M.D. New Eng. J. Med. 293: 521-524, 1975.

Studies of the clinical value of the limulus amebocyte lysate test for the detection of endotoxemia are inconsistent. In an attempt to define the value of this test, a total of 237 plasma samples from 111 patinets were tested for endotoxin with seven different lysate preparations. A total of 48 plasma samples yielded a positive test with one or more of the seven preparations. Two of eight samples positive with all seven preparations were from ambulatory patients. A significant positive correlation of the test with bacteremia, neutrophilia and elevated serum alkaline phosphatase was found. Only three of the 48 positive tests occurred by four hours of incubation, and only 12 were associated with positive blood cultures (eight contained gram-negative bacteria). The test now available has no clinical usefulness in the detection of endotoxemia or gram-negative septicemia. (New Engl. J. Med.)

61. Plasma expansion in surgical patients with high central venous pressure (CVP); the relationship of blood volume to hematocrit, CVP, pulmonary wedge pressure, and cardiorespiratory changes. Se-Min Back, M.D., Gilbert G. Makabali, M.D., Christopher W. Bryan-Brown, M.D., Joyce M. Kusek, R.N., and William C. Shoemaker, M.D. Surg. 78: 304-315, 1975.

There was no correlation of blood volume measurements with central venous pressure (CVP) or hematocrit determinations and only minimal suggestive trends with wedge pressure in a large series of postoperative patients; the lack of correlations emphasize the unreliability of venous pressure and hematocrit determinations to predict blood volume alterations. To evaluate the physiological problems, to define optimal therapeutic goals, and to measure therapeutic effectiveness of volume loading with an oncotically active agent, we measured the hemodynamic and oxygen transport responses to 500 ml. of 5 percent albumin give over 1 hour in 22 patients.with CVP greater than 15 cm. H_2O. The patients were separated into two groups according to the CVP response to volume therapy. The CVP decreased in 14 (64 percent) of these patients (Group 1), but it increased slightly but not significantly in eight (36 percent) patients(Group 2). In Group 1 patients, there was increased flow, improvement of tissue perfusion

as reflected by increased oxygen consumption, and augmentation of the ventricular function. In Group 2 there were slight increases in mean flow, mean pulmonary arterial pressure, and mean transit time and slightly decreased pulmonary vascular resistance; there was appreciable improvement in left ventricular function without significant deterioration of right ventricular function. The high initial central venous pressure is not a reliable index of either hypervolemia or cardiac failure in critically ill patients. It is concluded that a trial of volume loading with an oncotically active agent with frequent auscultation of the chest and careful observation of the CVP trends will give the maximum diagnostic as well as therapeutic information.

62. Editorials - Glucagon and Shock. Samuel Vaisrub, M.D. Jama, 233: 1195, 1975.

Whatever its physiologic role in normal glucose metabolism, glucagon now occupies center stage alongside insulin in the pathophysiologic drama of diabetes mellitus. The excess of glucagon, which invariably accompanies diabetic ketoacidosis, may play as important a part in causing gluconeogenesis, ketogenesis, and lipolysis as does the lack of insulin.

Hyperglucagonemia also occurs in stressful conditions that are related not to diabetes, but to shock. A number of investigators have published reports on the observed rise in serum glucagon levels in shock associated with major trauma, extensive burns, severe infection, and myocardial infarction. What is the mechanism of hyperglucagonemia in shock? Is the hyperglucagonemia in shock harmful or beneficial?

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